Monoclonal Antibodies to Endotoxin in the Management of Sepsis

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New monoclonal antibodies directed against the lipid A moiety of the endotoxin present in gram-negative bacteria have been developed to improve the clinical outcome in patients with sepsis. Two studies of monoclonal antibodies HA-1A and E5 retrospectively identified specific patient subgroups showing benefit with therapy. I analyze and summarize the new sepsis nomenclature, the structure of endotoxin, the data implicating endotoxin as a causative agent in septic patients' morbidity and mortality, and specific data from the 2 clinical studies of monoclonal antibody therapy.

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Sepsis remains among the most difficult and frustrating management problems in critical care medicine. Despite aggressive measures using costly technology, the available treatment of patients with sepsis still results in an unacceptably high mortality. With the development of antiendotoxin monoclonal antibodies, the question for physicians is whether these new therapies will change the morbidity or mortality of this disorder.* Two new monoclonal antibodies have been produced against the lipid A moiety of the endotoxin component of gram-negative bacterial cell walls, in the hope that blocking lipid A would prevent the manifestations of sepsis. Recent controlled trials using the HA-1A (Centocor, Inc, Malvern, Pennsylvania) and E5 (Xoma Corporation, Berkeley, California) monoclonal antibodies in septic patients have identified subgroups of the study populations who had statistically significant decreases in mortality and improvement in the recovery of organ dysfunction after early administration of these monoclonal antibodies versus placebo. The characteristics of the subgroups benefiting from treatment in the two studies differ, however, and important questions remain as to which product is useful in these patients or whether either drug is of enough benefit to warrant its high cost.

I will review the following concepts:

- The proposed sepsis nomenclature to classify patients who have sepsis or the sepsis syndrome,
- The structure of endotoxin and the manipulations of its biochemical milieu that allow the development of monoclonal antibodies to the lipid A component of endotoxin,
- The experimental observations regarding endotoxin infusion into animals and humans,
- The correlation between the serum detection of endotoxin and blood cultures positive for gram-negative bacteria in septic patients, and
- The discrepancies between two clinical trials using monoclonal antibodies directed against lipid A.

*See also "Therapies Directed Against Endotoxin—Has the Time Come?" by Z. M. N. Quezado, MD, and W. D. Hoffman, MD, on pages 424-425 of this issue.

Definition of Sepsis

Many clinicians use the term "sepsis" to refer to patients who have evidence of infection and hemodynamic instability. Until recently, no attempts had been made to standardize the various terms used interchangeably, including bacteremia, septicemia, sepsis, and septic shock. In 1989 Bone and co-workers proposed a new set of broad definitions that described sepsis more completely. Specifically, bacteremia defines blood cultures positive for bacterial pathogens; sepsis refers to a condition of high suspicion or an obvious source of infection, accompanied by fever or hypothermia, tachypnea, and tachycardia; the sepsis syndrome requires evidence of altered organ perfusion—metabolic acidosis, elevated lactate levels, renal failure with oliguria, hypoxemia, and altered mental state—in addition to sepsis, but does not require positive blood cultures; and, finally, septic shock refers to patients with the added complication of hypotension and can be further classified as refractory if it persists for more than an hour despite fluids and pressor support.[1]

Gram-negative Bacteria and Endotoxin

The clinical progression of infection that leads to hemodynamic collapse and death has been described as the sepsis cascade.[2] A source of infection such as pneumonia or abscess may result in the release of bacterial toxins into the bloodstream. These toxins may be either bacterial products such as staphylococcal enterotoxin or components of the cell walls, including endotoxin. These toxins can enter the bloodstream and interact with the cells of

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ABBREVIATIONS USED IN TEXT
Ig = immunoglobulin
LPS = lipopolysaccharide

the immune system, causing the release of endogenous mediators such as interleukins and tumor necrosis factor. The interaction of all these mediators causes cardiovascular insufficiency as a result of a depressed left ventricular ejection fraction, left ventricular dilatation, and increased permeability of the vascular endothelium. Hypotension and decreased end-organ perfusion may result, possibly leading to death.

Gram-negative bacteria account for a substantial proportion of the infections that cause this sepsis pathophysiology, but other infectious agents initiate the same sequence of events that may lead to shock and death. Both gram-positive and gram-negative bacteria produce the same pattern of cardiovascular changes associated with sepsis in dogs.[3] The essential difference between gram-positive and gram-negative bacteria lies in the structure of their cell walls; endotoxin is absent from the cell wall of gram-positive bacteria, which comprises mainly peptidoglycans and techoic acids. Endotoxin has been shown not to be the universal mediator of septic shock, as dogs infected with gram-positive bacteria did not have evidence of endotoxin but showed the same cardiovascular changes as in gram-negative sepsis. It is important to remember that the presence of endotoxin is sufficient but not necessary to cause sepsis.[3] Many investigators continue to search for the final common mediator in the pathway of injury leading to sepsis.

Endotoxin, a lipopolysaccharide found in the outer membrane of gram-negative bacteria, consists of three main regions. The highly variable oligosaccharide, or "O region," conveys antigenic specificity to different types of gram-negative bacteria and can activate the alternate pathway of complement. The R-core region is less variable among different gram-negative bacteria; therefore, antibodies to this region can be cross-protective against infection caused by different gram-negative bacteria. The lipid A component of the cell wall is the most highly conserved region and is considered the toxic element of endotoxin; it can stimulate the release of tumor necrosis factor and can directly activate the classical pathway of complement activation.[4] The new monoclonal antibodies are thought to bind to lipid A, thereby blocking its activity.[5]

Experimental infusion of endotoxin into animals and humans produces the same systemic responses and cardiovascular changes associated with sepsis, supporting its role as a mediator in sepsis. In animals, endotoxin infusion causes fever, the release of interleukin-1 and tumor necrosis factor, complement activation, disseminated intravascular coagulation, and shock.[4] In humans, after a 45- to 60-minute quiescent period, the infusion of endotoxin may cause an acute-phase response with fever, arthralgias, myalgias, headache, and nausea; this occurs within two to three hours of infusion and usually subsides by five to eight hours. Administering endotoxin also results in a hyperdynamic cardiovascular state with a depressed and dilated left ventricle and reversible abnormalities of ventricular performance and volume. In addition, the infusion of endotoxin causes alterations in pulmonary function and gas exchange and activates the fibrinolytic system.[6]

Evidence exists against an important role for endotoxin in sepsis. Mice have different sensitivities to endotoxin, varying by as much as 5,000-fold, yet all have a similar lethal response when infused with live gram-negative bacteria.[7] Human volunteers can be vaccinated against endotoxin, but when given typhoid or tularemia, they were not protected clinically from these illnesses.[8] Finally, the measurements of endotoxin in the serum of patients who have gram-negative sepsis have not consistently correlated with the clinical manifestations or outcomes.[9]

Endotoxemia and Positive Blood Cultures

The rationale for therapy with the new monoclonal antibodies to endotoxin assumes the presence of endotoxin in the serum of all patients with gram-negative sepsis. Recently the chromogenic limulus lysate assay was used to detect serum endotoxin, based on the ability of endotoxin to activate a proenzyme that cleaves a *p*-nitroaniline group from the chromogenic substrate.[10] Investigators studied 110 patients with shock; 100 had shock resulting from infection, and 10 had nonseptic causes of shock. Only 43 of the 100 septic patients had endotoxin in their serum; the assay was positive in 20 patients on the first serum specimen, and in the other 23 patients it became positive within the first 20 hours after study entry. Most of the 43 patients had multiple serum specimens positive for endotoxin, and in all patients who recovered, the endotoxin had cleared from their bloodstream. Endotoxin was uncommon in patients with nonseptic causes of shock, such as cardiac failure; only 1 of 10 patients with nonseptic shock had detectable endotoxemia. In addition, the presence of endotoxin in the 43 septic patients was significantly associated with blood cultures positive for bacteria, lactic acidemia, decreased systemic vascular resistance, and depressed left ventricular function—all features consistent with a clinical diagnosis of sepsis.

Subgroup analysis of the patients who had both endotoxin detected in their serum and positive blood cultures revealed that only 26% of patients with positive blood cultures had gram-negative bacteria—that is, gram-negative bacteremia never developed in 74% of patients with endotoxemia. This suggested that endotoxin may be present when the patient does not have gram-negative bacteremia. Conversely, 14% of patients without endotoxin had gram-negative organisms grown from their blood, implying that endotoxin may be rapidly cleared from the bloodstream. Further, endotoxin was detected in the serum of 12 of 18 patients who had blood cultures positive for gram-positive bacteria and fungi, suggesting that there may have been undetected coincident gram-

negative infection or that endotoxin leaked from another focus of infection. Overall, the subgroup of patients with both endotoxin detected in their serum and blood cultures positive for all pathogens had a substantial increase in the occurrence of renal failure, the adult respiratory distress syndrome, and death.

The results of this study demonstrate an inconclusive relationship between endotoxemia and the isolation of gram-negative bacterium in the blood of patients with sepsis. Most patients with septic shock did not have detectable endotoxin in their blood; this may result from infection with pathogens other than gram-negative bacteria, the rapid clearance of endotoxin, or local sequestration of the endotoxin. Most patients with endotoxemia never had cultures positive for gram-negative bacteria, suggesting that endotoxin can persist even after the clearance of bacteria from the blood or that there may be other sources of endotoxin leaking into the circulation. These studies confirm that the presence of endotoxin is sufficient but may not always be a part of the pathogenesis of sepsis.[10]

Monoclonal Antibodies to Endotoxin

Antibody to intact endotoxin, the complete lipopolysaccharide (LPS) portion of the gram-negative outer membrane, is directed primarily against the highly variable O-region side chains, which differ greatly between different strains of gram-negative bacteria; such an antibody would protect against the effects of LPS from one bacterial strain but would be much less effective against LPS from other bacterial strains. Antibodies to the lipid A moiety, however, the most highly conserved region of LPS among various gram-negative bacteria, should be protective against all gram-negative organisms.

Investigators circumvented the problem of antigenic diversity of the gram-negative bacteria by using a gram-negative bacterium containing only the core and lipid A elements, devoid of the variable side chains.[11] The J5 mutant of *Escherichia coli*, 0111:B_4, lacks the enzyme uridine 5′-diphosphate-galactose 4-epimerase and cannot incorporate the exogenous galactose into LPS; this epimerase deficiency prevents the attachment of side chains. The J5 mutant contains only the core determinants of LPS, including lipid A, *N*-acetylglucosamine, 2-keto-3-deoxyoctonate, heptose, and glucose.[11]

In rabbits immunized with the J5 mutant, high levels of antibody to J5 LPS developed; they were protected against a Shwartzman reaction using purified endotoxins from other bacteria including *E coli*, *Salmonella typhimurium*, and *Neisseria meningitidis*. Neutropenic rabbits treated with J5 rabbit antiserum had increased survival compared with controls when given gram-negative infections. In contrast, antiserum to the intact LPS of the parent *E coli* strain, in which the core elements are concealed by the O side chains, did not confer protection against infection by other bacteria; J5 antiserum adsorbed by J5 LPS was also ineffective, but antiserum to purified lipid A-rich J5 LPS was fully cross-protective.[11]

In 1982 human J5 antiserum was prepared by vaccinating healthy men with heat-killed *E coli* J5.[11] In a randomized, controlled trial, it was found that human antiserum to J5 resulted in a statistically significant decrease in mortality in patients with bacteremia and shock.[11] In 1985 the human J5 antiserum was given prophylactically to surgical patients; while it had no effect on the incidence of gram-negative infections, there was a statistically significant reduction in both the incidence of shock and the mortality in patients with shock, especially in the group requiring abdominal operations.[12]

Although antiserum against the modified LPS of the *E coli* J5 mutant showed clinically significant reductions in morbidity and mortality in rabbits and humans, the specific type of antibody conferring benefit was still unknown. In 1988 an IgG-purified antibody from pooled plasma obtained from volunteers immunized with the *E coli* J5 mutant was used in a double-blind, randomized study of patients with gram-negative infections.[13] There was no difference in mortality between the patients given the *E coli* J5 immunoglobulin (Ig) G antibody versus controls given standard IgG antibody. It was concluded that IgG antibody was not responsible for the protective benefits of the antiserum.[13] Finally, in the same year with the use of another type of mutant LPS from *Salmonella minnesota*, it was reported that the protective activity of the antiserum resided in the IgM antibody and that the IgG antibody did not bestow protection.[14] The subsequent development of the monoclonal antibody to the *E coli* J5 mutant LPS has obviated the need for the difficult and costly establishment of a reproducible supply of human antiserum and has avoided the risks of disease transmission from the parenteral use of human blood products.

The evaluations of the two monoclonal antibodies to the endotoxin component of the *E coli* J5 mutant have now been reported. The HA-1A monoclonal antibody developed by Centocor and the E5 monoclonal antibody developed by Xoma were studied in prospective, multicenter, randomized, double-blind placebo-controlled trials. They both used clinical features similar to those of the "sepsis syndrome" definition as the inclusion criteria: evidence of clinical infection with changes in vital signs and altered end-organ perfusion.[5,15] In both studies, patients were observed for 28 days or until death.

Both agents are IgM antibodies, but the HA-1A is a human product and E5 is a murine product. The antibodies HA-1A and E5 both act against the lipid A moiety of a wide variety of gram-negative bacterial endotoxins. The administration of HA-1A to study patients included a single 100-mg dose of the drug given within a mean time period of 14 hours after study entry; E5 was given in two doses, the first dose of 2 mg per kg within 8 hours of meeting the entry criteria, followed by the second dose 24 hours later.

The determination of drug efficacy depended on the specific identification of subgroups defined differently in the two studies. In the first, positive blood cultures were used to define "bacteremia," and the second used the term "sepsis" to refer to a positive culture from speci-

mens of blood or a body fluid.[5,15] Both studies evaluated the drugs' effects on mortality and on the resolution of organ failure.

The results from the HA-1A study demonstrating drug efficacy are based only on the subgroup of 200 patients who had blood cultures positive for gram-negative bacteria, or 37% of the 543 patients in the entire study group. The antibody HA-1A was given to 262 patients, and 281 patients received placebo. The sources of infection were primarily in the genitourinary and gastrointestinal tracts, and the most common pathogens included *E coli* and *Klebsiella, Enterobacter,* and *Pseudomonas* species. In the subgroup of patients with bacteremia, there was a notable decrease in mortality in patients treated with HA-1A; 32 of 105 patients died (30%) compared with 45 of 92 control patients who died (49%), for an overall reduction in mortality of 39% ($P = .014$). Further subdividing the group of patients with bacteremia into two subgroups with and without shock showed a statistically significant decrease in mortality in both groups. In the group with shock, death occurred in 18 of 45 patients (33%) treated with HA-1A compared with 27 of 47 control patients (57%), for an overall 42% reduction in mortality ($P = .017$). In the group without shock, 14 of 51 patients (27%) treated with HA-1A died compared with 18 of 45 control patients (40%), an overall reduction of 33% (Table 1).

TABLE 1.—*Reduction in Sepsis Mortality Using Monoclonal Antibodies to Endotoxin*

Patient Population	Mortality, No. Patients Died / No. Infected (%)		
HA-1A study: Subgroup with bacteremia (n = 200)*			
	Overall	*Without Shock*	*With Shock*
Placebo.....	45/92 (49)	18/45 (40)	27/47 (57)
HA-1A	32/105 (30)	14/51 (27)	18/45 (33)
E5 study: Subgroup with sepsis (n = 316)†			
	Overall	*Without Shock*	*With Shock*
Placebo.....	62/152 (41)	27/63 (43)	36/89 (40)
E5.....	62/164 (38)	22/74 (30)	41/90 (45)

*The HA-1A (Centocor, Inc, Malvern, Pa) study showed efficacy only in the subgroup of patients identified retrospectively with gram-negative bacteremia, defined as positive blood cultures. A statistically significant reduction in mortality occurred in all patients of the subgroup, in both those with and without shock ($P < .05$).

†The E5 (Xoma Corp, Berkeley, Calif) study showed efficacy only in the subgroup of patients identified retrospectively with gram-negative sepsis, defined as gram-negative bacteria detected in cultures of either blood or body fluid. A statistically significant reduction in mortality occurred only in the patients without shock ($P = .01$); there was no reduction in mortality in the subgroup overall or in the subgroup with shock.

Substantial organ-system failure—manifested by shock, disseminated intravascular coagulation, acute renal failure, acute hepatic failure, or the adult respiratory distress syndrome—occurred in 123 of the 200 patients with gram-negative bacteremia. During the first seven days after treatment, the complicating conditions resolved in 26 of 62 patients given placebo (42%), compared with 38 of 61 patients given HA-1A (62%) ($P = .024$), showing a significantly greater resolution of organ failure.

There was no protection by HA-1A in patients with focal nonbacteremic gram-negative infection and in the patients without any evidence of gram-negative bacterial infection. In the entire study group of 543 patients, there was no statistically significant reduction in mortality overall. In summary, HA-1A therapy reduced mortality only in the subgroup of study patients who had blood cultures positive for gram-negative bacteria, whether the patients were normotensive or in shock. The drug also enhanced the resolution of organ-system dysfunction in this same subgroup of patients with gram-negative bacteremia.[5]

The initial E5 study enrolled 486 patients with a systemic response to infection suspicious for a gram-negative bacterial cause,[15] but analysis of the data focused on the 316 patients with gram-negative sepsis defined as a positive blood or body fluid culture. In the group of patients with gram-negative sepsis, there was no overall reduction in mortality. In the subgroup of patients with sepsis and shock, the E5 antibody also did not reduce mortality. The E5 antibody showed a statistically significant reduction in mortality only in the subgroup of patients with sepsis who were normotensive; death occurred in 43% of control patients compared with 30% of patients treated with E5 ($P = .01$). Of note, the benefit of E5 in this subgroup of patients without shock occurred regardless of whether the qualifying culture with a gram-negative bacillus was from blood or another body fluid (see Table 1).[15]

The preliminary analysis, however, of a second trial of E5 in 847 patients, performed to test the hypothesis that E5 benefits patients who had gram-negative sepsis but were not in shock, did not show improved survival in the 530 patients with documented gram-negative sepsis.[16] A trend toward improved survival was seen in a subgroup of 139 treated patients who had major-organ failure without refractory shock.

A reduction in organ failure also resulted from therapy with E5 in the first study, but again only in the same subgroup of patients with gram-negative sepsis who were normotensive; 19 of 35 (45%) patients treated with E5 had improved organ function, but only 8 of 27 (30%) of control patients had improvement ($P = .05$).[15] There was no reduction in organ failure in patients with sepsis and shock. In summary, administering E5 reduced mortality in the subgroup of study patients who had positive cultures of blood or body fluid, but only if they were not in shock. The drug did resolve organ system dysfunction, but again in the subgroup of patients with sepsis who were not in shock.

Both drugs had rare reported side effects of hives, flushing, rash, and transient hypotension. Patients treated with HA-1A reportedly did not have the development of antibodies to the HA-1A drug, whereas anti-mouse antibodies to the murine drug did develop in 47% of patients treated with E5.

Discussion

Therapy directed against the endotoxin component of the gram-negative bacterial cell wall is based on evidence that the infusion of endotoxin into animals and humans

results in clinical manifestations and hemodynamic changes similar to those that occur in sepsis. Because it is known that other infectious agents such as gram-positive bacteria may cause the same pathophysiology, endotoxin is a sufficient but not a necessary factor to cause sepsis. The presumed universal mediator of the final common pathway of sepsis remains elusive.[3]

Preliminary studies with antiserum to endotoxin from the *E coli* J5 mutant in animals and humans led to the elaboration of specific monoclonal antibodies of the IgM class directed against the lipid A moiety of LPS for use in clinical trials of patients with evidence of gram-negative bacterial infection. Monoclonal antibodies to endotoxin prevent sepsis by blocking the interaction of the toxic lipid A moiety with the body's cellular defenses.

Understanding the implications of the studies by Ziegler and Greenman and colleagues using two monoclonal antibodies requires a familiarity with the definitions of the patient subgroups in these studies. Ziegler and co-workers used the term bacteremia to identify those patients who had blood cultures positive for gram-negative bacteria; Greenman and associates used the term sepsis to refer to those patients who had positive blood cultures or positive body fluid cultures. Although bacteremia is a stricter definition requiring the detection of the pathogen in the blood and thus implying the simultaneous presence of endotoxin in the serum, the broader term sepsis as used by Greenman and colleagues includes the possibility that endotoxin may be present in the blood as the result of a leak from a focal site of infection, without confirmation of bacteria in the blood. Of note, the entry criteria for both studies are similar to the definition of the sepsis syndrome proposed by Bone, which does not require that there be blood cultures positive for bacteria.

Retrospective analysis of both trials suggests that therapy, initiated at study entry before final culture results, only benefits patients with gram-negative bacterial infection and cultures of blood or body fluids positive for such. Unfortunately, most clinicians are too familiar with the need for aggressive empiric therapy for all patients with deteriorating clinical conditions consistent with sepsis, usually before culture results can be obtained. Thus, a prospective selection of candidates for these therapies will be difficult because no clinical features predict the subsequent development of bacteremia.[17,18]

Both studies showed drug efficacy in patients who had positive cultures by reduced mortality and by the association with resolving organ failure. The two studies using similar products had two different results, however. Administering HA-1A benefited all patients with gram-negative bacteremia who were treated with the drug, regardless of the presence of shock. Giving E5 benefited patients with cultures positive for gram-negative bacteria only if they did not have shock in the initial study; even this result was not confirmed in a follow-up study using E5. The reasons for these different results are not explained by the manufacturers of either drug. Therefore, the data from these studies are inadequate to lead to a reasonable clinical decision as to which drug to use.

Ongoing analyses of the data from the HA-1A study and the two E5 studies question the conclusions of efficacy in the subgroups who appeared to benefit from therapy.[19] A detailed independent analysis of the second E5 study may clarify the results that failed to confirm the drug efficacy found in the first study. Critics who challenge the efficacy of using HA-1A in patients with gram-negative bacteremia suggest that administering HA-1A may, in fact, benefit only patients with gram-negative bacteremia who are in shock. Other concerns about the HA-1A study focus on the following:

- The number of patients receiving inadequate antimicrobial therapy in the placebo group is disproportionate,
- Raw APACHE II scores were used instead of individual risks,
- The differences in the time of administering HA-1A or placebo possibly influenced outcome;
- The antibody HA-1A had its effect primarily in patients at study centers with high case-fatality rates for gram-negative bacteremia, and
- The HA-1A group had a higher mortality compared with the placebo group in patients who had nonbacteremic gram-negative infections.[19]

Ziegler refutes these criticisms, noting that licensure has been unanimously recommended by a United States Food and Drug Administration advisory panel, and rejects the suggestion that additional placebo-controlled trials to demonstrate efficacy are warranted.[20]

Finally, the data from the study by Danner and coworkers shed doubt on the correlation between blood cultures that are positive for gram-negative bacteria and the presence of endotoxin in the serum.[10] Neither monoclonal antibody study reported the measurement of serum endotoxin levels. The data from this study did not show a correlation between an early detection of endotoxin and a later development of gram-negative bacteremia. As previously noted, only 26% of patients with detectable endotoxemia had blood cultures positive for gram-negative bacteria—that is, most never had a positive blood culture. In addition, 14% of the patients without endotoxemia had cultures positive for gram-negative bacteria, implying that endotoxin may be rapidly cleared from the bloodstream. Overall, most of the patients with sepsis in this study never had detectable levels of endotoxin. Either endotoxin from gram-negative bacterial infection exists only transiently in the blood or other mediators may be more important in the initiation of the sepsis cascade.[10] Therefore, the detection of endotoxin cannot be used in the process of deciding whether to use these drugs.

Other investigators have voiced concerns about the safety of the monoclonal antibodies.[21,22] A trend toward increased mortality was noted among patients without gram-negative bacteria in the treatment group, raising the possibility that HA-1A may have unrecognized toxic-

ity.[21] The potential for the development of human antibodies against the foreign antibodies has also been addressed.[15,22] The antibody E5 is a murine product developed by the fusion of murine splenocytes immunized against the J5 mutant of *E coli* with murine myeloma cells; HA-1A is the product of the fusion of human spleen cells and a mouse-human heteromyeloma.[22] None of the 116 patients treated with HA-1A in the series reported by Ziegler and co-workers had detectable levels of anti–HA-1A antibodies using a double-antigen radiometric assay with a sensitivity of 3.5 μg of antibody per milliliter of serum.[5] In the study by Greenman and associates, antimurine antibodies appeared late in 86 of 182 patients (47%) treated with E5; a standard enzyme immunoassay with a sensitivity of less than 1 ng per ml was used to detect antibodies, and the researchers defined a response as occurring when a fourfold increase over baseline titer was detected.[15] The failure of the Ziegler group to detect anti–HA-1A antibodies may have resulted from limited sampling and the use of a less sensitive assay, since none of the patients' antibody responses to E5 were as high as 3.5 μg per ml, the threshold for detection in Ziegler's assay.[15] The possibility of antibodies developing to either monoclonal antibody has as-yet-unknown implications for the subsequent administration of the drug or for the use of other murine products.

Finally, some authors have anticipated the magnitude of the additional costs of introducing an expensive new therapy into the arsenal of critical care medicine. An additional expenditure of $1.6 billion has been estimated for HA-1A based on the current incidence of gram-negative bacteremia, the percentage of Ziegler and co-workers' patients with gram-negative bacteremia, and a conservative cost estimate of $2,000 per patient.[17]

A sophisticated economic assessment was made of the use of HA-1A based on the results of the study by Ziegler and colleagues.[23] Issues of concern to clinicians were addressed by a cost-effectiveness analysis based on the following:

- A cost of $3,750 per dose was based on a recently established price for HA-1A in the Netherlands;
- The HA-1A therapy might affect acute-care hospital costs, resulting in a calculated incremental cost of $19,200 for the care of each additional survivor benefiting from HA-1A therapy (excluding the drug cost);
- Adjusted life expectancies were incorporated to reflect comorbid conditions in patients with sepsis, yielding an average gain of five years of life per survivor; and
- Two treatment models were used to illustrate the effects of liberal or strict criteria for administering the drug; the first model assumes treatment with HA-1A for all patients with sepsis, and in the second model patients receive HA-1A only if they have positive results from a hypothetical test that can determine the presence of endotoxemia or gram-negative bacteremia before therapy is instituted.

It was concluded that HA-1A therapy alone might cost $1.5 billion annually, resulting in an overall increase of $2.3 billion to national health care costs. Cost-effectiveness ratios reveal a cost of $24,100 per year of life gained if all patients with sepsis are treated; this compares favorably to the use of colestipol hydrochloride as a cholesterol-lowering therapy at $91,280 in 1991 dollars and to the use of zidovudine in asymptomatic patients with the human immunodeficiency virus at a range of $6,553 to $70,526. If a test (estimated at $100 in the model) could identify all patients with endotoxemia or gram-negative bacteremia before therapy is started (thus limiting the use of the agent), then potentially the cost per year of life saved could be reduced from $24,100 to $14,900, with an overall savings of $1 billion.[23] It appears that factors such as drug cost, the influence of comorbid conditions on survival benefits, and the variability of hospital costs all directly affect the possible cost of HA-1A therapy in sepsis; but the analysis suggests that a restricted use of HA-1A in a prospectively identified group of patients with gram-negative sepsis has the greatest potential for containing health care costs.

In conclusion, therapy for sepsis with monoclonal antibodies directed against the lipid A moiety of endotoxin of gram-negative bacteria has been shown to have limited efficacy in a subgroup of patients identified retrospectively. The discrepancy between the studies of HA-1A and E5 remains unanswered. More investigation is required before these drugs can be used in all patients suspected of having gram-negative sepsis.

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LETTER FROM HOME

If I had a butler
I'd call him Contumely
and yet forgive him
the tray of toast he brings
dry as these bones I inhabit.
My body's insults bruise my tea,
here and now under the apple
and the pear.
Then I had such a long fall
yesterday, half the length
of the stairs, and now
the outrageous spring.
What little I've had of butlers
left years ago before
the liver spots.
They *say* it's spring again.
It must be. I hear the tink
tink, tink of nutbirds.
I am delighted the trillium
you sent me before the fall
survived the winter.
My keeper is scornful.
Small and insignificant
she says, but doesn't know
the miracle of survival,
tight in my mind.
The enclosed check is for your
daughter's daughter—please forward.
May I have a new address soon?
I send much love. Trillium.

THOMAS C. BUELL©
Portland, Oregon